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Botulinum toxin type A in the treatment of focal, axillary and palmar hyperhidrosis and other hyperhidrotic conditions

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Focal essential hyperhidrosis is a common and often disabling disorder mainly involving the palms, axillae, face, and soles of the feet. Focal hyperhidrosis may also arise from several neurological or internal diseases. Current therapeutic options include topical aluminium chloride salts, systemic anticholinergic drugs, tap-water iontophoresis, and a number of surgical approaches. However, none of these are entirely satisfactory. In recent studies, injection of botulinum toxin type A (BTX-A) into the hyperhidrotic area has proved very effective in reducing or abolishing focal sweating of different aetiologies without major side effects. BTX-A therefore has the potential to replace more invasive therapies. Eur J Neurol 6 (suppl 4):S111–S115 © Lippincott Williams & Wilkins

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INTRODUCTION

Physiology of sweating

There are two types of sweat glands: the 'apocrine' glands and the 'eccrine' glands (Sato, 1977; Sato *et al.*, 1989a,b). The apocrine glands are mainly localised in the axillae and the perianal region, where they constitute 10–40% of the regional sweat glands; they are not active until puberty. They may have specialised functions such as pheromone production but they are not involved in thermoregulation (Ogawa, 1984; Ogawa and Low, 1993). In contrast, the eccrine glands are involved in normal temperature regulation and these sweat glands are responsible for hyperhidrosis. However, the areas affected by focal essential hyperhidrosis, usually the palms, soles and axillae, are responsible for only 10% of the body's thermoregulatory capacity. Eccrine glands cover most of the body and have a density of approximately 60/cm^2, except on the palms and soles, where their density is much greater, at approximately 600/cm^2 (Sato, 1997). Eccrine sweat glands consist of a secretory coil connected by a duct to the surface. They are innervated by post-ganglionic cholinergic sympathetic neurons termed sudomotor fibres. It is this cholinergic innervation which can be targeted by botulinum toxin type A (BTX-A) to block sweating. By contrast, apocrine glands are innervated adrenergically and are unaffected by BTX-A.

Definition of hyperhidrosis

Focal hyperhidrosis can be defined as excessive sweating of the palms, soles of the feet, axillae, and face. It can be both a distressing and a genuinely disabling condition. Focal hyperhidrosis is reported to affect up to 0.5% of the population and usually manifests itself during the second or third decade of life. The simple qualitative definition of hyperhidrosis as excessive sweating is, of course, completely subjective. Measurements of the rate at which some sufferers sweat reveal that they have enormous water loss, in the range of litres/day, which is well beyond normal levels. A quantitative definition of hyperhidrosis as the production of more than 50 mg of sweat in one palm or axilla per minute has also been suggested for use in studies and when examining the effects of therapeutic intervention.

Pathophysiology and classification of hyperhidrosis

Hyperhidrosis can be classified as focal or generalised. The most common form of focal hyperhidrosis is essential or idiopathic focal hyperhidrosis, resulting from over-activity of the sweat glands of the palms, axillae, soles of the feet, and face. In 60–80% of the patients, the palms and soles of the feet (palmoplantar hyperhidrosis) are affected, and in 30–40%, the axillae are affected (Naver and Aquilonius, 1997). Facial sweating is less frequent. Focal hyperhidrosis may also arise following spinal cord injury and from some polyneuropathies. Gustatory sweating, also called Frey's syndrome, is focal sweating on the cheek in response to salivatory stimuli. This is the result of misdirection of autonomic nerve fibres after surgery of the parotid gland or is associated with some other rare conditions.

Generalised hyperhidrosis, typified by sweating occurring over the whole body, has many causes, and can be secondary to a variety of conditions, including metabolic diseases such as diabetes or hyperthyroidism, chronic infections like tuberculosis, alcoholism, and malignancy. The consequences of hyperhidrosis include dehydration and maceration of the skin, which may result in secondary skin infections.

The cause of essential focal hyperhidrosis is unknown at present. The sweat glands and their innervation do not show any histological abnormalities (Sato *et al.*, 1989a,b). Dysfunction of the central sympathetic nervous system is suspected, possibly involving hypothalamic nuclei, or prefrontal areas or their connections (Sato *et al.*, 1989a,b). Sufferers display no other signs or symptoms of autonomic dysfunction. A positive family history for the condition in 30–50% of cases suggests a genetic component (Mosek and Korczyn, 1995).

CURRENT TREATMENT OPTIONS

If there is no causal disease or if the underlying disease cannot be controlled sufficiently, there are numerous therapeutic approaches, although none are completely satisfactory.

Topical treatments

Current first-line treatment for focal hyperhidrosis is usually topical application of acids, aldehydes and metal salts. Aluminium chloride salts in alcoholic or aqueous solutions are the most widely used metal salts. However, one of the main limitations of aluminium chloride treatment is that, for efficacy, it needs to be applied regularly to dry skin. The mechanism of action of aluminium chloride is not fully understood. The reduction in sweat might be the result of damage to the terminal sweat ducts, or of binding of aluminium ions to the keratin of epithelial cells lining the lumen of the terminal sweat ducts, resulting in their closure.

Oral treatments

Anticholinergic drugs are quite effective but have unpleasant side effects such as dry mouth and blurred vision. Unfortunately, for many of these agents, the severity or incidence of side effects frequently outweigh the benefits.

Tap water iontophoresis

Tap water iontophoresis is a procedure in which the hands are soaked in tap water through which an electric current is passed for up to 30 min. The effect is an immediate decrease of sweat secretion with an initial duration of action of 3–4 days in most cases. In the beginning, the treatment is repeated several times, but once control is achieved a single treatment can be effective for several weeks. Iontophoresis is thought to be effective because ions block the sweat ducts.

Surgery

Many hyperhidrosis sufferers eventually resort to surgery. Excision and suction curettage of sweat glands are sometimes used in the axillae to remove the sweat coils in the skin. However, these methods may produce excessive scar formation and cannot be applied to the palms.

The neuronal innervation of the sweat glands in the palms can be blocked by destroying the second and third thoracic ganglia in a thoracic sympathectomy operation, resulting in correction of hyperhidrosis. Since the introduction of transthoracic endoscopic sympathectomy, this operation has become the treatment of choice in severe cases of hyperhidrosis as it provides lasting relief in many cases. However, there may be some serious complications, including pneumothorax, compensatory sweating in other areas of the body, or Horner's syndrome (Quinn *et al.*, 1993; Claes and Drott, 1994; Drott *et al.*, 1995). In one study, at a median of 13 months post-surgery, 56% of patients reported some, and 9% of patients reported severe, compensatory sweating (Graham *et al.*, 1996).

BTX-A IN THE TREATMENT OF FOCAL HYPERHIDROSIS

Hypo- or anhidrosis is a well-known effect of botulism and was described by the German romantic poet and physician Justinus Kerner in 1822 (Kerner, 1822). It was also noted as a side effect of BTX-A used in

TABLE 1. Published studies of borulinum toxin type A (BOTOX® and Dysport®) treatment of focal hyperhidrosis

Reference	Site	Number of patients	Total dose per site	Duration of anhydriotic effect
Naumann *et al.*, 1997b	Palms	1	30 U BOTOX®	> 3 months
Schnider *et al.*, 1997	Palms	11	120 U Dysport®	> 3 months
Naver and Aquilonius, 1997	Palms, axillae	7	28–78 U BOTOX®	> 1–8 months
Naumann *et al.*, 1998b	Palms, axillae, feet	11	30–50 U BOTOX®	> 5 months
Glogau, 1998	Axillae	12	50 U BOTOX®	4–7 months
Shelley *et al.*, 1998	Palms	4	100 U BOTOX®	4–12 months
Oddersen *et al.*, 1998	Axillae	2	50 U BOTOX®	NA
Heckmann *et al.*, 1998	Axillae	6	400 U Dysport®	> 4.5 months
Bergmann *et al.*, 1998	Trunk (Ross syndrome)	1	15 U BOTOX®	6 months
Naumann *et al.*, 1998a	Palms	20	50 U BOTOX®	NA

NA, Not available

the treatment of hemifacial spasms. These observations formed the basis for the development of BTX-A as a therapy for hyperhidrosis. Subsequently, BTX-A was able to abolish physiological sweating in the axilla and the back of the hand for 6–11 months in healthy volunteers (Bushara and Park, 1994).

The first report of BTX-A use in a patient with hyperhidrosis was published as a case history in 1997 (Naumann *et al.*, 1997b). A 26-year-old woman with a 10-year history of hyperhidrosis, but no other signs of autonomic dysfunction, had no lasting response to classic treatments such as iontophoresis and topical aluminium chloride. BTX-A (BOTOX® 100 U/3.0 ml normal 0.9% saline; Allergan Inc., Irvine, CA, USA) was injected into both palms at 10 different sites (3 U/site), each located approximately 2.5 cm apart. The effect of BTX-A was measured by pre- and post-treatment comparison of sweating in both palms using the Minor's iodine–starch test. The first anhidrotic areas were noted 24 h after injection of BTX-A, and hyperhidrosis was abolished 1 week after treatment, with no recurrence during the 14-week follow-up period. The only reported side effect was pain upon injection. A slight but transient decline in the force of hand-grip was measured upon testing 2 weeks after treatment.

Following this anecdotal report, several studies were undertaken (Naver and Aquilonius, 1997; Schnider *et al.*, 1997; Naumann *et al.*, 1998a,b; Odderson, 1998; Shelley *et al.*, 1998), and nearly 100 further effectively treated cases were published. The majority of these studies were performed in axillary and palmar sweating; only one was performed in patients with plantar or trunk sweating. Table 1 provides details from the literature regarding the sites of injection, the doses used and the duration of action after injection of BTX-A for hyperhidrosis.

Palmar sweating

The positive effect of BTX-A on palmar hyperhidrosis has been demonstrated in several open studies (Naver and Aquilonius, 1997; Naumann *et al.*, 1998a,b; Shelley *et al.*, 1998) and by a double-blind placebo-controlled trial (Schnider *et al.*, 1997). BTX-A has been injected using a grid for orientation or by evenly distributing small amounts of the toxin over the palms. Total doses used were in the range 30–78 U BOTOX® (Allergan, USA) (or 120 U Dysport®, Speywood, UK) per palm. In three of the larger studies (Schnider *et al.*, 1997; Naumann *et al.*, 1998a,b), a significant reduction in sweating could be demonstrated after injection (Figure 1A,B), well in accordance with the subjective estimation of the patients (Schnider *et al.*, 1997). The duration of action varied between 4 and 12 months, but was mainly within the range 4–6 months. Side effects included small haematomas, slight transient weakness of small hand muscles due to diffusion of the toxin, and pain at the injection sites. The latter problem can be avoided by administering a local nerve block on the median and ulnar nerves at the wrist prior to injection.

Axillary sweating

There are several reports on the treatment of axillary sweating with BTX-A (Naver and Aquilonius, 1997; Glogau, 1998; Naumann *et al.*, 1998a,b). Most injections were administered intracutaneously using a grid for orientation with squares of 2×2 cm^2 or using multiple injections evenly distributed over the identified hyperhidrotic area. The doses required ranged from 28 to 50 U BOTOX® (or 400 U Dysport®) per axilla. This was sufficient in most patients to completely abolish axillary sweating (Figure 1C,D). The duration of the BTX-A action was at least 4 months and as long

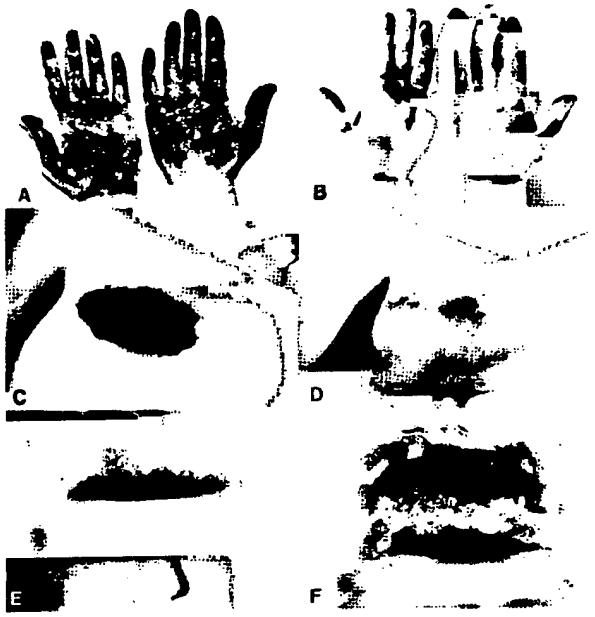

FIGURE 1. Palmar hyperhidrosis before (A) and after (B) botulinum toxin type A (BTX-A) injection of the left hand; axillary hyperhidrosis before (C) and after (D) BTX-A injection; facial hyperhidrosis before (E) and after (F) BTX-A injection. Staining of hyperhidrotic areas using Minor's iodine–starch test

as 7–12 months in some cases. Side effects included pain during the injections and small local haematomas.

Other conditions of focal sweating

BTX-A has also been applied to other conditions associated with increased focal sweating including facial hyperhidrosis, increased compensatory sweating in Ross syndrome (Bergmann *et al.*, 1998), and gustatory sweating (Nauman *et al.*, 1997a; Laskawi *et al.*, 1998).

Facial hyperhidrosis is a relatively rare form of essential focal hyperhidrosis that is also amenable to BTX-A treatment. The procedure corresponds to the approach in axillary and palmar hyperhidrosis, with single injections distributed over the forehead (Naumann, personal observation) (Figure 1E,F). In addition to those already mentioned, one side effect is the inability of the patient to frown after injection as a result of weakness of the forehead muscles. Ross syndrome is a rare disease of unknown aetiology characterised by progressive anhidrosis due to degeneration of sudomotor fibres. The disorder may be associated with disabling compensatory hyperhidrosis in areas in which sudomotor fibres remained intact. In this condition, BTX-A has proven effective in reducing the total amount of sweating (Bergmann *et al.*, 1998).

BTX-A has also been used as a highly effective treatment for gustatory sweating. In a study of 19 patients followed for 33 months, gustatory sweating returned in 12 patients and, based on subjective judgement, BTX-A had a mean duration of effect of 17.3 months (Laskawi *et al.*, 1998). In a second, larger study of 45 patients, there was a significant reduction of local facial sweating after injection of BTX-A, and no recurrence of sweating was observed during the follow-up period of 6 months (Naumann *et al.*, 1997a). Thus, BTX-A appears to have a particularly long-lasting effect on gustatory sweating, which may be related to the specific aetiology of the condition.

General observations

Irrespective of the injected site, the onset of action of BTX-A usually occurs within the first 3 days, and a maximum effect is generally seen within 1 week.

In a single study, efficacy and side effects of needle injections were compared with injections using a dermojet device (Naumann *et al.*, 1998a). Needle injection was more effective than the dermojet at the same doses. Side effects, particularly irritations of digital nerve branches, were more frequent with the dermojet, hence the dermojet cannot presently be recommended for BTX-A administration.

Effects of re-injection

This has not been examined in detail with respect to the use of BTX-A in hyperhidrosis. However, in our group, patients have been repeatedly injected over a period of 3 years with a relatively consistent and reproducible effect (Naumann, personal observation). In treating muscle spasms, one of the main concerns about repeated high-dose BTX-A injections is the triggering of an immune response to BTX-A, thereby generating neutralising antibodies. Although this is thought to occur in less than 4% of patients, re-injection should be avoided within 3 months after injection.

SUMMARY

All studies performed so far indicate that BTX-A is a safe and effective treatment for focal hyperhidrosis of the palms and axillae, of gustatory sweating, and of some other rare conditions associated with focal hyperhidrosis. At present, it appears that the duration of treatment is 4 months or longer, thereby exceeding the duration of BTX-A treatment of muscle contraction. The optimal and lowest dose for the treatment of axillary and palmar hyperhidrosis still needs

to be defined to minimise dose-related side effects, to lower the costs of treatment, and to reduce the risk of antibody formation. BTX-A should not be administered to pregnant or lactating women. In conclusion, BTX-A has the potential to replace current invasive and surgical techniques for the treatment of hyperhidrosis and should at least be considered as an alternative first-line drug treatment.

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